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Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1652

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: Lal et al.

Title: POLYNUCLEOTIDES ENCODING A HUMAN SODIUM-DEPENDENT
PHOSPHATE COTRANSPORTER (As Amended)

Serial No.: 09/991,212

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Examiner: Steadman, D.J.

Group Art Unit: 1652

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REPLY BRIEF ON APPEAL

Sir:

I. INTRODUCTION

This is Appellants' Reply Brief on Appeal (submitted in triplicate) in response to the Examiner's Answer dated November 4, 2003 ("the Examiner's Answer") in the above-identified application (the Lal '212 application).

On page 2 of the Examiner's Answer the Examiner states that the Appellants provide "a statement that all claims on appeal stand or fall together" (Examiner's Answer, page 2, § 7). The claims stand or fall together only with respect to issue 1. With respect to each of issues 2 through 4, different subgroups of the claims are grouped together for purposes of the Appeal, as indicated in the Brief on Appeal of August 13, 2003 (at page 4, § (7)), and as indicated in the Examiner's Answer under the "Grounds of Rejection" for each issue on appeal at, for example, pages 6, 8, and 12.

In addition, in the Examiner's Answer the Patent Examiner:

- (1) maintained the rejection of the claims on appeal under 35 U.S.C. § 101 on the grounds that the claimed polynucleotides are allegedly not supported by either a specific asserted utility or a well established utility,
- (2) maintained the rejection of claims 3, 6, 7, 9, 12, 13, 46, 48, 57, and 58, on appeal, under 35 U.S.C. § 112, first paragraph, for alleged lack of written description/possession of the claimed polynucleotide "variants" and "fragments,"
- (3) maintained the rejection of claims 3, 6, 7, 9, 12, 13, 46, 48, 57, and 58, on appeal, under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed polynucleotide "variants" and "fragments," and
- (4) maintained the rejection of claims 3-7, 9, 10, 12, and 57, on appeal, for alleged obviousness-type double patenting over claims 1-8 of U.S. Patent No. 5,985,604.

II. ISSUE 1 -- UTILITY REJECTIONS

A. Overview of Utility Rejections

In the rejections of the claimed invention for alleged lack of utility, the Examiner does not disprove the following:

- 1) that the claimed polynucleotide of SEQ ID NO:2, encoding the NAPTR polypeptide having the amino acid sequence of SEQ ID NO:1, is expressed in humans; and

2) that all, or almost all, polynucleotides expressed in humans have specific and substantial utility for measuring undesired side effects of drug candidates in toxicological testing.

It follows that the claimed invention is, by more than a reasonable probability, useful. There is no dispute that the Appellants need show no more than a reasonable probability that the claimed invention is useful to meet the requirements of 35 U.S.C. § 101 and § 112, first paragraph.

The Examiner never assails or even addresses this compelling logic. The Examiner continues to insist that the Appellants prove not only reasonable probability of utility, but also the biological or physical function of the claimed invention.

Nothing in the law requires the Appellants to prove biological function, and the Examiner does not point to anything in the law suggesting such a requirement. Indeed, the only law on this point is to the contrary: it is settled law -- and the Examiner does not rebut this -- that how an invention works (that is, its function) is utterly irrelevant to the utility analysis. In short, the entirety of the Examiner's argument is based on the confusion between, and improper equation of, use and function.

The Examiner apparently would rely on *In re Kirk* for the proposition that the Appellants must demonstrate biological function. *Kirk* requires no such thing. Indeed, *Kirk* is completely consistent with the requirement that the Appellants need only show utility of the claimed invention to reasonable probability. In *Kirk*, the applicant could not show reasonable probability because the only fact alleged by the applicant was that the claimed invention is a steroid. Because so many steroids -- indeed most of them -- have absolutely no use whatsoever, it followed that the applicant had not shown a reasonable probability of utility.

Application of the same logic to this case -- which the Examiner refuses to do -- yields a completely different result. In this case, the Appellants have identified the claimed invention as a member of a much better defined and narrower group: polynucleotides which encode proteins expressed in humans. As demonstrated above, because polynucleotides encoding proteins expressed in humans are predominantly useful, the Appellants can state with great confidence that the claimed invention is useful. How the invention actually works is utterly irrelevant to the analysis.

B. Responses to Specific Arguments by the Examiner

1. The Examiner contends on page 13 of the Examiner's Answer that "appellant's have failed to clearly demonstrate the polypeptide encoded by the claimed polynucleotide to be a member of the phosphate transporter family." The Examiner confuses function with use. These are not synonymous. It is irrelevant whether the SEQ ID NO:2 polynucleotide encodes a polypeptide that is a member of the phosphate transporter family, or that has the biological activities of phosphate transporters. The point for the purposes of the utility standard is that the polynucleotide encoding NAPTR, as a polynucleotide expressed in humans, is indeed useful for toxicology testing, drug discovery, and disease diagnosis.

Nevertheless, the specification discloses that the SEQ ID NO:1 polypeptide is a homolog of the human renal sodium phosphate transport protein NPT1, and thus that NAPTR is a member of the phosphate transporter family of proteins. In particular, the specification discloses that NAPTR and NPT1 share 48% sequence identity over 401 amino acid residues (Specification, e.g., at page 10, line 32 to page 11, line 1; and Figures 2A and 2B), and that NAPTR, NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter all share a potential N-glycosylation site (e.g., at page 11, lines 1-2), and have rather similar hydrophobicity plots (e.g., at page 11, lines 2-4; and Figures 3A, 3B, and 3C).

The Examiner continues the argument on page 13 (and also on pages 30-34 and 44-54) by asserting that "one of ordinary skill in the art clearly recognizes that the disclosed information in the specification merely *predicts or suggests* that the encoded polypeptide has phosphate transporter function based on a shared 48% identity to another phosphate transporter - this is far from a demonstration that the encoded polypeptide belongs to the phosphate transporter family or has phosphate transporter function" (Examiner's Answer, page 13; emphasis in original). The Examiner is incorrect in requiring that the phosphate transport function of NAPTR must be demonstrated unequivocally in order for the claimed invention to meet the utility requirement of 35 U.S.C. § 101. All that is necessary to meet the utility requirement is that a skilled artisan conclude that the claimed invention **more likely than not** has the asserted utility. Since a skilled artisan would reasonably conclude that the claimed polynucleotides would more likely than not have utilities based on the phosphate transport function of the encoded polypeptides, the utility requirement has been met.

The Examiner cites many references (e.g., on pages 30-34 and 44-54 of the Examiner's Answer), all of which have been previously addressed, to show that the biological function of the polypeptide encoded by the claimed polynucleotide cannot be predicted with certainty. However, all of these arguments fail to show that the claimed polynucleotide lacks utility because it is not necessary to predict biological function with certainty in order to meet the utility requirement of 35 U.S.C. § 101. In refusing to accept the "more likely than not" standard, the Examiner has inappropriately applied the cited references to the utility rejections.

2. The Examiner argues on page 13 of the Examiner's Answer that "there is no disclosure in the specification that this nucleic acid is expressed only in tumor or brain tumor tissue, nor does the specification disclose that the claimed nucleic acid has altered expression in tumor or brain tumor tissue as compared to normal tissue. Absent such a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, the gene is not a disease marker or an appropriate target for toxicology testing, drug development, and/or disease diagnosis" (Examiner's Answer, page 13). This is irrelevant. Appellants need not demonstrate whether the SEQ ID NO:2 polynucleotide is overexpressed or differentially expressed in any particular tissues, only that it is useful. The SEQ ID NO:2 polynucleotide is useful in toxicology testing whether or not it is overexpressed or differentially expressed in any particular tissues.

3. On page 14 (and again on pages 34-35), the Examiner refuses to accept the evidence of actual use and commercial success of the invention because "evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement" (Examiner's Answer, page 14). One reason that Incyte's customers subscribe to Incyte's sequence databases is so that they can purchase specific chemical compounds such as the polypeptides and polynucleotides described in the database. This is convincing evidence that credible, "real-world" utility exists for the claimed polynucleotides.

4. The Examiner argues on pages 14-17 that the utilities disclosed in the specification for gene and protein expression monitoring are not specific. The Examiner's argument amounts to nothing more than the Examiner's disagreement with the Bedilion Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the

Examiner's own judgment for that of the Appellants' expert. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the Bedilion Declaration demonstrates how one of skill in the art, reading the specification at the time the parent of the instant application was filed (February 24, 1997), would have understood that specification to disclose the use of the claimed polynucleotides in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the Bedilion Declaration at, e.g., ¶¶ 10-16).

5. On page 15 (and again on pages 20-25 and 35-36), the Examiner asserts that "[t]here is no clear indication that NAPTR is a target for drug development, toxicology studies, or disease diagnosis for . . . 'disorders associated with increased or decreased phosphate levels'. As such, additional research is required in order to ascertain the function of the encoded protein and/or identify a potential disease state or states which correlate with altered levels or forms of the claimed polynucleotide" (Examiner's Answer, page 15). Not so. The claimed polynucleotides can be used for toxicology testing in drug discovery regardless of whether the protein itself is a drug target. Monitoring the expression of the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide, or to a polypeptide encoded by such a polynucleotide, regardless of the disease association or biological function of the claimed polynucleotides. The claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to other polynucleotides and polypeptides, regardless of any possible utility for measuring properties of the claimed polynucleotides themselves.

6. The Examiner argues on page 15 (and again on pages 19-20 and 39-44) that use as a control for toxicology testing is not a specific utility because "any nucleic acid can be used as a probe - this utility is not specific to the claimed nucleic acid and instead applies to the broad class of nucleic acids" (Examiner's Answer, page 15). The Examiner doesn't point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of expressed polynucleotides can be so used, then they all have utility. The issue is, once again, whether the claimed invention has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of "well established" utilities presupposes that many different inventions can have the exact same utility. If the Examiner's argument

was correct, there could never be a well established utility, because you could always find a generic group with the same utility!

Furthermore, the Examiner is factually incorrect in stating that any new polynucleotide could be a probe used as a control for toxicology testing. The property of the claimed polynucleotides that makes them useful as controls for toxicology testing is their expression in naturally occurring cells. A polynucleotide having a random, non-naturally occurring sequence would most likely not be useful as a control for toxicology testing.

7. On page 17 of the Examiner's Answer, the Examiner asserts that "based on the Bedilion Declaration, one of ordinary skill in the art would recognize that knowledge of the function of the protein encoded by the claimed polynucleotide is necessary to be useful for gene expression monitoring in toxicology." Only some of the utilities discussed in the Bedilion Declaration are based on knowing the function of the protein encoded by the claimed polynucleotide. For example, the use of the claimed polynucleotide as a control in testing the potential toxicity of a drug candidate targeted to another polynucleotide is a specific, substantial, and credible utility that does not require any knowledge of the biological function or disease association of the claimed polynucleotide itself.

8. On pages 23-24 and 26, the Examiner refuses to consider that the claimed polynucleotide is a research tool, much like a scale, microarray, or gas chromatograph. The Examiner states that "a more representative analogy to the claimed polynucleotides and array would be that of a scale without an identifiable unit of measure - one could place an object on the scale, however, further experimentation would be required to interpret the result and determine the weight of the object" (Examiner's Answer, page 23). Once again, the Examiner has refused to consider that the claimed polynucleotide can be used as a research tool to study drug candidates targeted to other polynucleotides in toxicology tests. Such a use is separate from any study of the claimed polynucleotide itself.

9. The Examiner contends on pages 26-29 that the asserted utilities of the claimed polynucleotides in toxicology testing are not specific because "this is a utility that would apply to virtually every member of a general class of materials, such as any collection of polynucleotides. Thus, such a utility is *not* specific and does *not* constitute a 'well-established' utility" (Examiner's Answer,

page 27; emphasis in original). As discussed above (e.g., in § II.B.5), the claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to polynucleotides and polypeptides other than the claimed polynucleotides (and their encoded polypeptides). The effect of any particular drug candidate on the expression of any particular naturally occurring polynucleotide will be specific to both the drug candidate and the polynucleotide sequence. Such a toxicology test using an expressed polypeptide will differ from a toxicology test using any other expressed polynucleotide. Therefore, the asserted utility of the claimed polynucleotide in toxicology testing is credible, specific, and substantial.

10. The Examiner contends on pages 36 and 42 that “[i]t is noted that the specification provides no guidance regarding the meaning of any observed results of altered expression of the claimed polynucleotides . . . the specification provides NO indication as to whether a change in the expression of the claimed polynucleotides indicates toxicity or not and what level of altered expression would result in toxicity” (Examiner’s Answer, page 42). Dr. Bedilion in his Declaration states, and one of skill in the art would know, that “good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets” (Bedilion Declaration, ¶ 10 at page 8). Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide (or the polypeptide encoded by it) is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide sequence.

11. On pages 36-38, the Examiner takes issue with Appellants’ assertion that membership in a class of useful products can be proof of utility. The Examiner asserts that “the class of phosphate transport proteins cannot be used to predict utility for a new polypeptide that is included in the class based solely on sequence identity to another member of the class. Furthermore, there is no evidence of record to support an asserted specific and substantial utility or a well-established utility for the *entire* class of phosphate transporters” (Examiner’s Answer, page 37; emphasis in original). As discussed in the Brief on Appeal of August 13, 2003, the SEQ ID NO:1 polypeptide (encoded by the SEQ ID

NO:2 polynucleotide) could reasonably be considered to belong to the class of polypeptides consisting of phosphate transporters based on its structural homology to a known member of this class (e.g., human renal sodium phosphate transport protein NPT1). Furthermore, since all of the members of this class are useful as, for example, phosphate transporters that transfer phosphates across biological membranes, a skilled artisan would reasonably conclude that the SEQ ID NO:1 polypeptide was likewise useful.

C. Summary

It is true that just about any expressed polynucleotide will have use as a toxicology control, but Appellants need not argue this for the purposes of this case. Appellants argue only that this particular claimed invention could be so used, and have provided the Declaration of Bedilion to back this up. The Examiner is completely wrong to characterize Appellants' argument re: utility of a polynucleotide as a toxicology control somehow requires the person using the invention to do further research to identify the biological function or disease association of that polynucleotide. The point is not whether the invention is, in any given toxicology test, differentially expressed. The point is that the invention provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real world, for real purposes having nothing to do with further characterization of the invention itself.

III. ISSUE 2 -- WRITTEN DESCRIPTION REJECTIONS

A. Overview of Written Description Rejections

Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Appellants were in possession of the claimed polynucleotide variants and fragments. The Examiner instead states that "the single representative species of SEQ ID NO:2 fails to describe the entire genus of claimed nucleic acid

variants and nucleic acids *comprising* fragments of SEQ ID NO:2” (Examiner’s Answer, page 57; emphasis in original).

The Examiner’s position is contrary to the Patent and Trademark Office’s own written description guidelines (“Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001), which provide that:

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.** [footnotes omitted; emphasis added]

Here, there simply is no requirement that the claims recite the sequences of particular variants and fragments because the claims already provide sufficient structural definition of the claimed subject matter. That is, the claimed variants and fragments are defined in terms of SEQ ID NO:1 and SEQ ID NO:2. Because the claimed variants and fragments are defined in terms of SEQ ID NO:1 and SEQ ID NO:2, the precise chemical structure of every variant within the scope of the claims can be discerned. The Examiner’s position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention.

B. Responses to Specific Arguments by the Examiner

1. The Examiner asserts on page 57 of the Examiner’s Answer that “Appellants’ alleged description of variants of SEQ ID NO:2 and nucleic acids encoding variants of SEQ ID NO:1 and nucleic acids comprising fragments of SEQ ID NO:1 . . . merely provides a textual description of said variants and nucleic acids comprising fragments and provides no additional structures of representative species.” The Examiner is incorrect. The claims recite, for example, polynucleotide variants which comprise “a naturally-occurring polynucleotide sequence at least 90% identical to the polynucleotide

sequence of SEQ ID NO:2" and polynucleotide fragments comprising at least 20 contiguous nucleotides of a polynucleotide "consisting of nucleotides 1183 through 1154 of the polynucleotide sequence of SEQ ID NO:2." In these examples, the polynucleotide sequence of SEQ ID NO:2 is explicitly disclosed in the Specification at, for example, the Sequence Listing. The "textual description" of variants "at least 90% identical" to SEQ ID NO:2, in combination with the explicit disclosure of the SEQ ID NO:2 sequence, adequately appraises a skilled artisan of the structures of such variants. Likewise, the "textual description" of fragments of "at least 20 contiguous nucleotides" of an explicitly disclosed portion of SEQ ID NO:2 adequately appraises a skilled artisan of the structures of such fragments. The Examiner is incorrect in asserting that a "textual description" would not allow a skilled artisan "to visualize the structures of each member of the claimed genus" (Examiner's Answer, page 57).

2. The Examiner asserts on page 57 of the Examiner's Answer that "due to the substantial variation of species within the genus - it is highly unpredictable as to whether all species within the genus will encode polypeptides having the asserted phosphate transport activity." From this assertion, it appears that the Examiner would require that every single member of the genus of claimed polynucleotides have phosphate transport activity in order for there to be an adequate written description of the genus. Not so. To meet the written description requirement of 35 U.S.C. § 112, first paragraph, one of skill in the art need only reasonably understand that the inventors had possession of the claimed invention at the time the application was filed. It is not necessary that every member of the claimed genus have phosphate transport activity in order for the claimed invention to meet the written description requirement.

The Examiner continues by stating that "[a]t the time of the invention, one of skill in the art would recognize the absence of the ability to predict the function(s) of all species of claimed nucleic acids. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Examiner's Answer, page 59). However, the Examiner has not shown that the degree of unpredictability in the art is so high as to preclude an adequate written description of the claimed genus. Nor has the Examiner shown that the variation between the species of the claimed genus is so wide as to preclude an

adequate written description. The Examiner has only made unsupported assertions that the written description is inadequate.

Furthermore, the Examiner is incorrect in contending that “only one species within the genus” has been disclosed. The SEQ ID NO:2 has been explicitly disclosed by the recitation of its entire chemical structure. Based on this chemical structure, the structures of the recited polynucleotide variants and fragments have also been disclosed. For example, based on the SEQ ID NO:2 framework, the explicit chemical structure of every member of the claimed genus of polynucleotide fragments can be discerned.

3. The Examiner asserts that the claimed genus of polynucleotides has not been “sufficiently described by structure, physical properties, and chemical properties. The claimed genus has been described ONLY by a structural feature and the single disclosed species of SEQ ID NO:2 fails to represent all members of the claimed genus” (Examiner’s Answer, page 59). However, the Examiner has not provided any argument or evidence as to why this is so. The claimed polynucleotides have been described by physical properties (e.g., occurrence in nature of the recited variants species) and chemical properties (e.g., phosphate transport activity of the recited polypeptide fragments), in addition to the description by structure. The Examiner has not provided any substantive rebuttal of this; he has only made unsupported assertions that the claimed genus has not been described by structure, physical properties, and chemical properties.

4. In discussing the degree of variation within the claimed genus of polynucleotides, the Examiner asserts that “appellants have failed to provide convincing evidence that NAPTR itself is a phosphate transporter. Thus, it is unpredictable as to whether even those sequences encoding polypeptides sharing a relatively high degree of sequence homology with NAPTR with have phosphate transport activity,” citing van de Loo et al., Seffernick et al., Broun et al., and Scott et al. (Examiner’s Answer, page 60). However, the Examiner seems to have missed the point. For the purposes of determining the degree of variation among the members of the claimed genus of polynucleotides, it is irrelevant whether sequences having a high degree of sequence homology with NAPTR have phosphate transport activity. The Brenner reference was cited by the Appellants as an example of how a skilled artisan would view degrees of variation within a genus of polynucleotides or polypeptides. As

demonstrated by the Brenner reference, sequence identity as low as 30% can indicate structural homology, indicating that a genus of polypeptides could reasonably have variation of as much as 70% of the amino acid residues. Therefore, the Brenner reference is evidence that the claimed genus of variants, having sequence identity of at least 90% and variation of at most 10% of the amino acid residues, has a low degree of variation. As such, there is an adequate written description of the claimed genus of polynucleotides.

5. The Examiner emphasizes that “[m]ost importantly, one skilled in the art would not be able to divine the functions of other naturally-occurring sequences or nucleic acids comprising fragments of SEQ ID NO:2 based on the knowledge of the asserted function of only one disclosed species” (Examiner’s Answer, page 61). It is not necessary to “divine the functions” of all members of the claimed genus of polynucleotides because the description of the claimed polynucleotide variants and fragments in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2 satisfies the written description requirement of 35 U.S.C. § 112, first paragraph.

C. Summary

The Examiner has asserted that the function and/or sequence of each of the claimed polynucleotide variants and fragments must be provided in order for there to be an adequate written description of the claimed genus. However, this is not true. The Patent Office guidelines state that an adequate written description can be provided by “complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics” (P.T.O. Guidelines, *supra*; emphasis added). Therefore, there is no absolute requirement to provide the function and/or sequence of every claimed polynucleotide. The claimed polynucleotides have been described by chemical structure (e.g., relation of the recited polynucleotides to SEQ ID NO:2, relation of the recited polypeptides to SEQ ID NO:1), physical properties (e.g., occurrence in nature of the recited variant sequences), and chemical properties (e.g., phosphate transport activity of the recited polypeptide fragments). Therefore, the written description requirement has been met.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

IV. ISSUE 3 -- ENABLEMENT REJECTIONS

In maintaining the rejection of the claimed polynucleotide variants and fragments for alleged lack of enablement, the Examiner continues to insist that only those polynucleotides encoding polypeptides which are certain to have phosphate transport activity are enabled by the specification. The Examiner asserts that “nowhere does the specification provide guidance as to how to make and use those encoded polynucleotides encoding polypeptides having function other than the asserted phosphate transport activity, i.e., non-functional polypeptides and polypeptides having a biological activity other than phosphate transport” (Examiner’s Answer, page 64). This is incorrect. One of ordinary skill in the art would reasonably understand how to make and use the claimed polynucleotides, even if those polynucleotides encoded polypeptides having biological activities other than phosphate transport, or even if those polynucleotides encoded polypeptides having no biological activity. For example, the claimed polynucleotides can be used as hybridization probes.

The Examiner asserts that enablement as hybridization probes is not sufficient, stating that “the function of the nucleic acids comprising fragments of SEQ ID NO:2 is not limited to a hybridization probe and, from the specification, it appears that an intended use of the claimed nucleic acids is for protein expression” (Examiner’s Answer, page 73). However, to meet the enablement requirement of 35 U.S.C. § 112, first paragraph, it is only required that the claimed invention be enabled for one use. The claimed polynucleotides are enabled since a skilled artisan could use them as hybridization probes; it is not necessary to also enable the claimed polynucleotides for protein expression.

With respect to the use of the claimed polynucleotides to detect polynucleotides encoding NAPTR, the Examiner contends that “the claims are not limited to those polynucleotides having substantially similar structures that would be so useful - see for example, the polynucleotide of claim 13” (Examiner’s Answer, page 62). The Examiner is incorrect. Taking the Examiner’s citation of claim 13, the claim recites polynucleotides comprising at least 20 contiguous nucleotides of a portion of SEQ ID NO:2, and polynucleotides derived from such fragments (such as complements, variants, and RNA

equivalents). Contrary to the Examiner's assertions, polynucleotides comprising at least 20 contiguous nucleotides of the recited portion of SEQ ID NO:2 can be used to detect the SEQ ID NO:2 polynucleotide by hybridization, without undue experimentation. The Examiner insists that the full scope of the claims is not enabled by the specification, and yet fails to indicate how or why the recited fragments and/or variants of SEQ ID NO:2 could not be used as, for example, hybridization probes.

The Examiner asserts that "an endless amount of experimentation is required to determine the hybridization conditions and those nucleic acids that would hybridize under such conditions" (Examiner's Answer, page 63; emphasis added). Surely, this is an exaggeration. Based on the disclosure in the specification, and the state of the art at the time the application was filed, a skilled artisan would reasonably understand how to use the claimed polynucleotides as, for example, hybridization probes, without undue experimentation. The Examiner has not provided any evidence or sound scientific reasoning to support the assertion that a skilled artisan could not use the claimed polynucleotides in such a manner. For at least the above reasons, the enablement rejections should be overturned.

The Examiner also seems to take issue with the use of the term "comprising" in the claims. In particular, the Examiner states that "[t]he claims encompass nucleic acids encoding variants and nucleic acids comprising fragments that have the asserted phosphate transport activity in addition to variant polypeptides that are non-functional or exhibit a function other than the asserted phosphate transport activity" (Examiner's Answer, page 62; emphasis in original). The Examiner's emphasis seems to imply that the use of the transitional phrase "comprising" in the claims requires that the specification provide enablement for any possible element which could be a part of, but is not essential to, the claimed subject matter. However, the transitional phrase "'[c]omprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." M.P.E.P. § 2111.03 (citing *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997)).

The specification has provided enablement for polynucleotides comprising the recited polynucleotide fragments and variants. For example, the specification provides enablement for

polynucleotides comprising the recited polynucleotide fragments and variants as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:2 (Specification, e.g., at page 6, line 30 to page 7, line 16; page 11, lines 22-31; page 12, lines 5-22; page 20, lines 6-13; page 31, lines 6-26; and Examiner VI at page 40). One of skill in the art would understand how to make and use polynucleotides "comprising" the recited fragments and variants, without an explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter.

Furthermore, the Examiner contends that "the specification provides no teachings as to how to interpret the results of an expression analysis for toxicology testing" (Examiner's Answer, pages 62-63). This appears to be a reiteration of the Examiner's arguments regarding the utility rejection. Based on the arguments presented in the Brief on Appeal, the Declaration of Bedilion, and above (e.g., in § II), the claimed invention has at least one patentable utility that was well established at the time of filing of the parent of the instant patent application (February 24, 1997). One of ordinary skill in the art would know how to use the claimed invention as, for example, a toxicology control in drug discovery. As discussed above, there is no evidence that a skilled artisan would doubt that the claimed polynucleotides could be used for conducting toxicology tests of compounds during drug discovery.

Moreover, the Examiner continues to insist that Appellants have failed to demonstrate that NAPTR has phosphate transport activity. A skilled artisan would reasonably conclude that the SEQ ID NO:1 polypeptide has phosphate transport activity, based on homology to known phosphate transporters. Such a conclusion is supported by the teachings of Brenner et al. (Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078; of record), which speaks to the general applicability of using sequence homology as low as 30% over 150 amino acid residues to indicate protein homology, and Bork (Genome Res., 2000, 10:398-400; of record), which teaches that the prediction of functional features by homology has a 90% accuracy rate (Table 1 of Bork).

The Examiner attacks the use of these references, asserting that a skilled artisan would not apply the teachings of Brenner et al. (1998) to the instant case, and that "Bork does not remove the

high degree of unpredictability that is inherent in mutating or altering a protein-encoding polynucleotide” (Examiner’s Answer, page 66). The Examiner insists that there is a “high” degree of unpredictability in functional annotation, and that the degree of unpredictability is so high as to preclude the enablement of the claimed invention. However, the Examiner has provided to evidence to support such assertions. Appellants are not arguing that “a high degree of unpredictability does *not* exist when one alters or varies a protein-encoding polynucleotide” (Examiner’s Answer, pages 66-67). Appellants argue only that the degree of unpredictability is not so high as to preclude enablement of the claimed polynucleotides.

For example, in discussing the Broun reference, the Examiner states that “[w]hile the four mutations of Broun et al. did not *completely* convert the desaturase activity to a hydroxylase activity, the mutations as taught by Broun et al. nonetheless led to the generation a novel activity for their desaturase, thus providing support for the unpredictability of modifying an encoding nucleic acid” (Examiner’s Answer, page 67). The Examiner remains focused on the unpredictability of making mutations as opposed to the question of enablement. The Broun example demonstrates that the degree of unpredictability in making mutations is not so high as to preclude enablement of variant polypeptides and polynucleotides because the polypeptide of Broun et al. can still be used in the same way as the parent polypeptide, i.e., as a desaturase. In this example, it is irrelevant that mutations introduced a novel activity because a skilled artisan would still be able to use the mutant polypeptide, without undue experimentation, based on the knowledge of the desaturase activity of the parent polypeptide.

In addressing the Seffernick reference, the Examiner refuses to accept that the enzymes are functionally similar. In particular, the Examiner ignores that there is at least one member of the amidohydrolase superfamily that catalyzes both deamination and dechlorination reactions with triazine ring substrates (e.g., Seffernick et al., page 2409, right column, second paragraph). This is evidence that the melamine deaminase and atrazine chlorohydrolase of Seffernick are functionally similar, and thus that the degree of unpredictability in making mutations is not so high as to preclude enablement of polypeptide variants based on functional annotation.

The Examiner's arguments focus on the unpredictability of making mutations in polypeptides. Appellants acknowledge that there is some degree of unpredictability in making mutations. However, such unpredictability is not so high as to preclude enablement of the full scope of the invention because there is no requirement that all of the claimed polynucleotides encode functional polypeptides. Polynucleotides which are structurally related to SEQ ID NO:2 (including polynucleotides comprising fragments and/or variants of SEQ ID NO:2) can be used as hybridization probes to detect the SEQ ID NO:2 polynucleotide, regardless of the biological activity of those polynucleotide fragments and variants. The Examiner has provided no evidence or sound scientific reasoning to show that the claimed polynucleotides could not be used in such a manner.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

V. ISSUE 4 -- OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

Appellants request that the requirement for submission of Terminal Disclaimers with respect to the '604 patent be held in abeyance until such time that there is an indication of allowable subject matter. The Examiner has acknowledged this request (Examiner's Answer, page 74).

VI. CONCLUSION

For all the foregoing reasons and the reasons stated in the Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

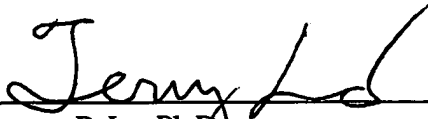
If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108.

This form is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

Date: December 23, 2003


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